Cumulative Tar Exposure

A New Index for Estimating Lung Cancer Risk Among Cigarette Smokers

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A new index for estimating lifetime exposure to tar from cigarette smoking was found to be the best measure of the relative risk for Kreyberg type I (KI) and Kreyberg type II (KII) lung cancer in a case–control study of 2296 cases (1274 KI and 1022 KII) and 4667 controls. There is a steep, near-linear dose–response of lung cancer risk of both histologic types to cumulative exposure to tar, although the odds ratios are three to five times higher for KI than for KII. The odds ratios for lung cancer in women are consistently higher than those in men with the same level of exposure to tar, particularly among long-term smokers who smoke heavily. Based on their estimates of odds ratios associated with tar exposure, the authors projected an approximate 15–20% decrease in KI lung cancer risk among long-term smokers who smoked heavily for every 10-mg decrease in tar in the cigarettes they smoked. *Cancer* 1992; 70:69–76.

Key words: dose–response, Kreyberg I and Kreyberg II lung cancer, odds ratio, tar yield, pack-years.

The risk of cancer is obviously influenced by the dose of a carcinogen. The fact that this applies to tobacco smoke as well was established decades ago.[1,2] We also learned early on that the epidemiology of lung cancer in terms of susceptibility to tobacco smoke and possibly other factors differs according to sex and histologic type.[1-5] In this study, we evaluate the effect of lifelong tar exposure on the risk for lung cancer according to histologic type and sex.

Through our analyses, we re-examine the relative risk of the histologically characterized Kreyberg type I (KI) (squamous, epidermoid, oat, and small and large cell cancers) and Kreyberg type II (KII) (adenocarcinoma) lung cancers in relation to lifetime exposure to cigarette tar and attempt to quantify the decrease in risk of KI lung cancer that may result from smoking cigarettes with lower tar yields. (We used KI and KII terminology recognizing that there may be some epidemiologic variations for each cell type.) We evaluate selected measures of risk from cigarette smoking that have been used by other investigators and compare them with estimates of exposure on the basis of the cumulative tar yield of all cigarettes smoked.

We believe our index of lifelong tar exposure is a comprehensive estimate of risk related to the major tobacco carcinogen (tar) because, in addition to the number of cigarettes smoked, it takes into account the substantial variation in tar yield among the different brands and the chronologic changes in the smoking habits of each individual.

Methods

The data were derived from a large data base collected for an ongoing hospital-based case–control study of tobacco-related cancers that was conducted in 26 hospitals in 6 cities in the United States.[3]

This study included 1274 patients with KI (813 men and 461 women) and 1022 with KII (567 men and 455 women) lung cancer admitted to the participating hospitals from 1981–1988. The KI cases included squamous cell, large cell, oat, and small cell carcinoma, whereas the KII cases included adenocarcinoma and alveolar cell carcinoma. The 4667 controls (2828 men and 1839 women) were selected from among patients with non-tobacco–related diseases and were matched to the cases according to age, sex, race, and time of admission. All data were collected using a detailed, standardized questionnaire that was completed by trained interviewers

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and included information on demographic factors, smoking history, medical history, and diet.[3] Smoking history included information on the brand of cigarette smoked, number of cigarettes smoked per day, and number of years each brand was smoked. The questionnaire had space for patients admitted from 1981–1984 to list up to four different brands of cigarettes, and for those admitted later to list up to seven. If the number of different types of cigarettes smoked exceeded these numbers, the tar yield and cigarettes smoked per day (CPD) were averaged over the brands that were not listed individually, and the duration of smoking was summed over them.

Ever smokers were defined as those who had ever smoked cigarettes at least once a day for 1 year. Current smokers were those who had smoked within the past year. Nonsmokers were those who had never smoked cigarettes regularly. Those who smoked pipes or cigars, either alone or in addition to cigarettes, were excluded from the data.

Lifetime exposure to cigarette smoking is estimated using pack-years, nonfilter and filter years, current number of CPD, and tar years.

Pack-years (P) is calculated as the number of cigarettes of each brand smoked per day (C), multiplied by the number of years that brand was smoked (Y). These products are summed over the different brands smoked throughout each participant's lifetime (B), and divided by 20 to convert the total into packs:

$$P = \sum_{i=1}^{B} (C_i \times Y_i \times 1/20).$$

The cumulative index that measures lifetime exposure to tar through cigarette smoking (T) is computed by summing over the different brands smoked (B) the products of tar content in milligrams (t), the number of days that brand was smoked (D), and the number of cigarettes of each brand consumed per day (C). The result is then converted into kilograms:

$$T = \sum_{i=1}^{B} (t_i \times D_i \times C_i) \times 10^{-6}.$$

Data on tar yield for each brand were obtained from the Federal Trade Register for the year 1977 for patients admitted from 1981–1984, and for the year 1988 for patients admitted thereafter.[6] Tar is defined as that portion of the mainstream smoke of a machine-smoked cigarette that is retained on a glass fiber filter, minus nicotine and water.[7]

Lung cancer risk was estimated using odds ratios and their 95% confidence intervals.[8] Adjusted odds ratios were calculated using the generalized Cochran–Mantel–Haenszel statistic.[9] Chi-square tests for trend[10] were conducted to evaluate the dose–response of risk over exposure level.

The data were maintained and analyzed with a VAX 11/750 minicomputer using a VMS operating system (Digital Equipment Corp., Maynard, MA). Statistical computations were performed using SAS software.[11]

Results

Comparison of Cases and Controls

The relative frequencies of race and age were approximately equal in KI and KII cases and controls and in both sexes (Table 1). However, the frequency of KI lung cancer decreased sharply as the level of education increased, especially among men.

Smokers had more than a 20-fold increase in the

Table 1. Case–Control Status According to Demographic Variables

	Men			Women		
	% Controls (n = 2828)	*% KI (n = 813)*	*% KII (n = 567)*	*% Controls (n = 1839)*	*% KI (n = 461)*	*% KII (n = 455)*
Race						
White	93.9	93.1	92.2	94.8	93.3	94.3
Nonwhite	6.0	6.9	7.8	5.2	6.7	5.7
Education (yr)						
< 12	25.2	38.5	29.2	22.2	26.3	20.7
12	27.6	30.9	27.8	39.2	42.0	43.3
13+	47.2	30.6	43.0	38.6	31.8	36.0
Age (yr)						
< 55	28.8	27.0	33.0	35.5	28.2	31.6
55–64	40.6	39.5	38.8	39.8	39.2	35.4
65+	30.6	33.6	28.2	31.8	31.9	33.0
Never smoked	29.0	1.7	6.5	51.1	4.8	13.4
Smoker	71.0	98.3	93.5	48.9	95.2	86.6

KI: Kreyberg type I; KII: Kreyberg type II.

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Table 2. Age-Adjusted Odds Ratios for Kreyberg Type I Lung Cancer

Measure of exposure to cigarette smoking	Men				Women			
	Quitters		*Current smokers*		*Quitters*		*Current smokers*	
	No.	OR	No.	OR	No.	OR	No.	OR
Cumulative tar exposure (kg)								
1–2	376	7.3	243	17.3	219	7.9	325	23.1
3–5	276	19.9	348	29.7	76	15.3	225	47.6
6–8	173	20.0	306	38.7	31	33.2	115	58.9
9+	169	38.3	374	60.2	33	22.9	69	102.9
Pack-years								
1–19	482	3.3	122	4.9	288	2.4	152	11.3
20–39	410	10.6	358	22.8	134	14.2	275	28.6
40–49	258	30.1	421	33.7	86	21.8	232	64.8
50+	259	37.7	485	60.9	49	32.3	120	92.2
Most recent CPD								
1–10	120	4.1	172	14.4	103	1.2	138	7.5
11–20	261	9.0	461	22.3	95	13.8	315	33.6
21–40	254	16.6	537	41.4	64	14.2	271	76.0
41+	172	23.5	218	74.0	22	12.4	57	153.9

OR: odds ratio; CPD: cigarettes smoked per day.

frequency of KI cancer, but only a 6-fold to 7-fold increase in the frequency of KII lung cancer when compared with those who had never smoked. When smokers at the lowest exposure levels are used as the reference group instead of those who had never smoked, the age-adjusted odds ratios for KI over increasing levels of tar exposure range from 2.3–4.5 for men and from 2.7–5.2 for women. For KII lung cancer the dose–response is substantially weaker, with odds ratios of 1.5–2.2 for men and 2.0–2.2 for women.

Association Between Lung Cancer and Exposure to Cigarette Smoking

Tables 2 and 3 summarize the risk of lung cancer associated with various measures of exposure to cigarette smoking. The odds ratios are adjusted to factor out the potential confounding effect of age with extent of exposure.

Tar exposure, pack-years, and current CPD all exhibit dose–responses, suggesting the presence of a

Table 3. Age-Adjusted Odds Ratios for Kreyberg Type II Lung Cancer

Measure of exposure to cigarette smoking	Men				Women			
	Quitters		*Current smokers*		*Quitters*		*Current smokers*	
	No.	OR	No.	OR	No.	OR	No.	OR
Cumulative tar exposure (kg)								
1–2	373	2.6	305	6.5	223	3.2	333	8.3
3–5	239	4.4	300	6.5	74	4.8	218	15.1
6–8	165	6.2	259	10.1	27	8.5	86	11.6
9+	105	7.3	278	12.8	21	6.8	42	16.3
Pack-years								
1–19	460	1.3	140	4.6	309	2.1	160	4.9
20–39	428	4.0	335	6.1	141	6.1	265	8.8
40–49	149	6.2	368	9.1	81	12.5	198	16.9
50+	219	8.8	358	13.0	42	7.8	94	22.6
Most recent CPD								
1–10	117	1.0	160	3.9	113	2.2	145	3.6
11–20	261	3.5	421	6.0	95	5.0	292	9.3
21–40	246	5.6	466	10.3	65	5.4	241	20.5
41+	213	4.6	155	15.8	19	1.8	42	30.5

OR: odds ratio; CPD: cigarettes smoked per day.

cause-and-effect relationship with risk for both histologic types of lung cancer.

The relationship between cigarette smoking and lung cancer is considerably less pronounced for KII than for KI. The odds ratios for quitters are substantially lower than those for current smokers, particularly at the highest levels of most recent CPD. Generally, women exhibit a higher risk for lung cancer of both histologic types at every level of exposure.

The age-adjusted odds ratios for tar exposure in current smokers are presented in Figure 1 according to sex and histologic type. The dose–response curves demonstrate that not only are the odds ratios for KI higher in women, but the difference between the sexes is greatest at the higher exposure levels (23–103 in women, compared with 17–60 in men). The corresponding difference in odds ratios is small for KII (8–16 in women and 7–13 in men).

Table 4 summarizes the differences in smoking patterns and the trends in cigarette smoking over time according to sex. The lower incidence of lung cancer in women[12] is clearly related to the fact that, on the average, women start smoking at a later age (20 versus 17 years), smoke fewer cigarettes per day (21 versus 27), and chose brands with lower tar yield (15 versus 18 mg per cigarette). Nevertheless, smoking is more common among women than men, and women are less likely to quit.[13] As demonstrated by the age-specific incidences of lung cancer listed in Table 4,[14] the differences in incidence of lung cancer between the sexes are gradually reduced in the younger age groups from a male to female ratio of 3.8 at 70 years of age or older, to 2.0 at 50–59 years of age. This apparent cohort effect on relative risk follows the gradual increase in the number of women who are smoking compared with men that has been observed over the past few decades. However, women continue to smoke fewer cigarettes and their

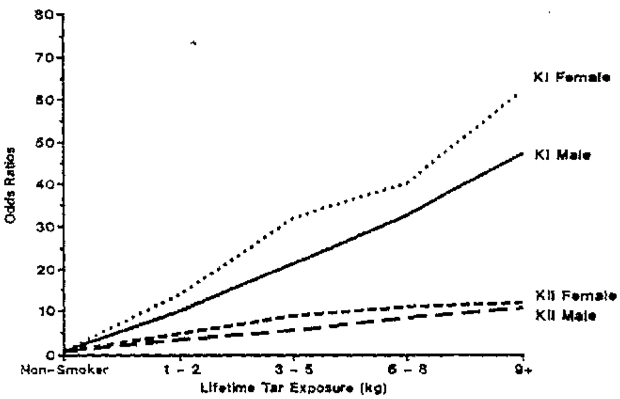

Figure 1. Age-adjusted odds ratios for lifetime tar exposure in current smokers were computed according to sex and histologic type, with a group who never smoked used as the reference group.

substantially higher rate of lung cancer, as shown for the years 1974–1985,[12] clearly exceeds the rate of change in their smoking behavior observed over time. In particular, the nearly three-fold increase in the relative frequency of the small cell histologic type in women, compared with no change in men,[15] is disproportionate to the earlier change in the male to female ratio for smoking exposure, as reflected by the concurrent estimates.[13]

In long-term smokers who have smoked for 30 or more pack-years, the projected reduction in risk for both types of lung cancer associated with every 10-mg decrease in tar yield per cigarette ranges between 15–20% (Fig. 2). However, the actual impact on disease prevalence is not as great for KII because the associated risk for this type of lung cancer is less than one-third of that for KI. Similarly, the proportionate decrease in odds ratios is expected to be greater among women than men because the latter appear to be less affected by exposure to tar.

Figure 3 shows the remaining dose–response of KI lung cancer risk over lifetime exposure to tar for current smokers, with four commonly used estimates of smoking exposure held constant at high levels: more than 30 years of smoking filter and nonfilter cigarettes, more than 40 pack-years of smoking, and more than 20 cigarettes currently being smoked per day.

Overall, the odds ratios are higher and the residual dose–response over lifetime exposure to tar is stronger in women than in men. The effect of increasing tar intake among those who smoke heavily is clearest when measured in those who smoke 21 cigarettes per day or more and long-term smokers of filter cigarettes. The dose–response in those who have smoked for 41 or more pack-years and long-term smokers of nonfilter cigarettes is clear only at the highest levels of tar exposure. Figure 3 indicates a twofold to fourfold difference in the odds ratio for KI lung cancer among those who smoke heavily, depending on their cumulative lifetime intake of tar.

Table 5 compares the age-adjusted estimates of dose–response in odds ratios for KI lung cancer among current smokers, with three measures of exposure held constant: lifetime tar, pack-years, and CPD. Both lifetime tar and pack-years exhibit a strong residual dose–response for both sexes; however, the clear trend over CPD shown in Table 3 is now largely cancelled out by the effects of the other two measures of exposure.

Discussion

Effect of Cumulative Tar Exposure

Of the various indices of exposure to cigarette smoking examined, lifelong exposure to tar represents the most

Table 4. Cigarette Smoking and Lung Cancer Trends by Sex

	Men	Women	Ratio (men to women)
Cigarette smoking			
Age began (x̄ ± SD)	17 ± 5	20 ± 6	0:9
CDP (x̄ ± SD)	27 ± 13	21 ± 13	1:3
Tar in mg/cigarette (x̄ ± SD)	18 ± 6	15 ± 6	1:2
Current smokers (%)*			
1974	42	31	1:4
1985	32	27	1:2
Quitters (%)*			
1974	41	32	1:3
1985	49	43	1:1
Never smoked (%) (55 years of age or older)	21	39	0:5
Lung cancer			
Incidence (per 10^5)†			
1974	74	20	3:7
1985	82	36	2:3
Age-specific incidence‡ (per (10^5) 1981–1985)			
50–59 yr	253	124	2:0
60–69 yr	366	157	2:3
70+ yr	522	138	3:8
Distribution by histologic type§ (%)			
Small cell,			
1974			
1985			
Large cell 1974	18	8	2:3
1985	17	30	0:6
Squamous	11	26	0:4
1974	19	7	2:7
1985	50	29	1:7
Adenocarcinoma	37	23	1:6
1974	20	37	0:5
1985	27	40	0:7

SD: standard deviation; CPD: cigarettes smoked per day.
* Fiore *et al.*[13].
† SEER data.[12]
‡ SEER data.[14]
§ El-Torky *et al.*[15]

comprehensive estimate of lung cancer risk associated with cigarette smoking.

Pack-years, a commonly used estimate of exposure, fails to account for the large difference in tar content among various brands. The discrepancy in risk estimates between pack-years and tar exposure is expected to broaden with time because an increasing proportion of smokers will have had the opportunity to smoke the low-yield cigarettes for an adequate number of years to have an effect on risk.

Risk estimates based on years of smoking filter versus nonfilter cigarettes, or their ratio,[16,17] also fail to consider the ever increasing variation in tar content within each category. These measures do not account for the individual differences in the number of CPD. In fact, as indicated by the results of several previous investigations,[18–20] a number of those who switch from high-yield to low-yield cigarettes are likely to increase their daily cigarette consumption, which tends to inflate risk estimates based only on the duration of smoking low-yield cigarettes.

CPD is inadequate as a measure of lung cancer risk, whether using the most recent level or averaging over a given number of years, because duration of exposure is an essential component of risk that cannot be ignored. This is demonstrated by the finding that ever smokers have lower risks than current smokers. Apparently, because ever smokers include both recent and longtime quitters, their average duration of smoking is expected to be shorter than that of current smokers.

Exposure to tar has been estimated by several previous investigators, notably Hammond et al.,[21] Lubin et al.,[22] Kunze and Vutuc,[23] Kaufman et al.,[24] and Stellman and Garfinkel.[25] Some of these investigators used

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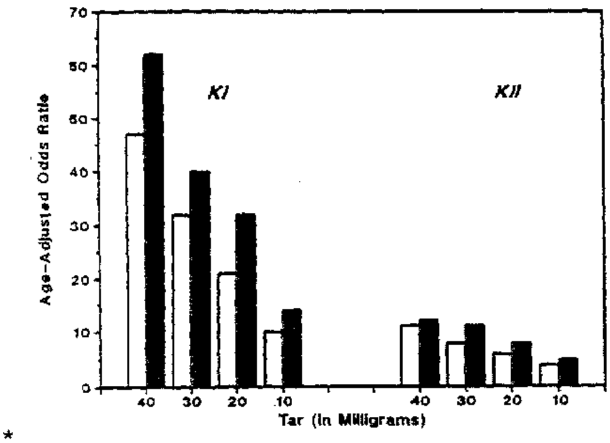

* After 30 pack-years

Figure 2. The age-adjusted odds ratios obtained for lifetime tar exposure were used to compute projected odds ratios for KI and KII lung cancer in men and women. The estimates assume 30 pack-years of cigarette smoking at various levels of tar yield, ranging from 10–40 mg per cigarette. □:Males; ■:females.

grouped levels of tar based on the most common brand smoked by each individual, without including measures of duration or the number of CPD of each brand.[21,22] Others calculated tar exposure by including CPD and duration of smoking, but categorized tar content as low, medium, or high instead of using the actual number of milligrams per cigarette.[21,23] Still others based categories of tar yield on the brand "usually" smoked; they controlled for CPD by categorizing them into grouped intervals, or alternated between the average tar content of every brand smoked by an individual and the tar content of brands smoked for a minimum of 10 years.[24]

The index of lifelong exposure to tar introduced here is unique because it incorporates the duration (in years) and the number of cigarettes smoked of each brand, multiplied by the amount of tar delivered in the smoke of each brand. Thus, the risk estimate reflects the total amount of tar available for inhalation to each individual during his or her lifetime.

Our finding that tar yield retains a strong residue of dose–response in KI lung cancer risk, even when other measures of exposure are held constant (Fig. 3), underscores that the difference in lung cancer incidence among long-term smokers who smoke heavily is, to a great extent, related to the difference in cumulative tar intake. For example, the steep dose–response over tar intake in long-term filter and nonfilter cigarette smokers indicated in Figure 3 reflects the wide individual variation in CPD and tar yield. The equally steep dose–response over tar intake among smokers of at least 21 CPD, however, is largely a reflection of differences in duration and type of cigarettes smoked. A dose–response also is present when pack-years are held constant because, although this measure incorporates both duration and CPD, it fails to allow for variations in tar yield. Furthermore, as mentioned above, because much time has passed since the introduction of low-yield brands, the reliability of pack-years as a measure of lung cancer risk will continue to diminish. The dose–response for KI lung cancer risk to CPD is largely obliterated by the effects of lifetime tar and pack-years (Table 5) because both duration and tar yield are omitted from this measure of exposure. Tar yield and pack-years both retain a clear residue of dose–response: one reflects the effect of cumulative tar intake and the other reflects the effect of duration of exposure.

Male/Female Differences in Risk

A consistent result that emerged from our analyses was that, given the same level of cigarette smoking exposure, the risk of both types of lung cancer, but especially of KI, is consistently higher for women than for men. The age-adjusted odds ratios (Table 3) are approximately one and one-half to two times higher in women than in men at the various levels of pack-years and lifelong exposure to tar and for both histologic types. The dose–response in odds ratios over lifelong exposure to tar, at constant levels of duration of smoking nonfilter and filter cigarettes, pack-years, and CPD, is far stronger in women than in men (Fig. 3); this suggests a greater susceptibility to the carcinogenic effect of tar itself.

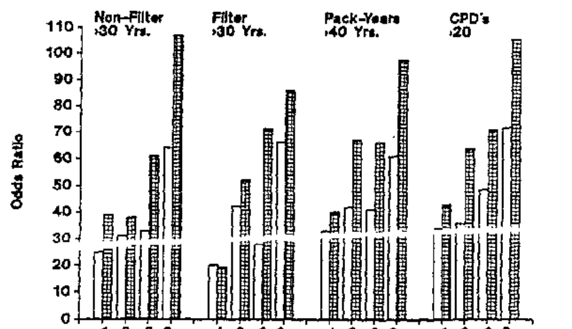

Figure 3. The residual dose–response in odds ratios for KI lung cancer over lifetime exposure to tar from cigarette smoking is estimated in current smokers, with four commonly used estimates of smoking exposure held constant: 30 or more years of smoking nonfilter or filter cigarettes, more than 40 pack-years of smoking, and 21 or more cigarettes currently being smoked per day. Separate estimates are computed for men and women. □:Males; ■:females.

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Table 5. Age-Adjusted Dose–Response Effect on Kreyberg Type I Lung Cancer With Other Exposures Held Constant

Lifetime tar (kg)	At ≥ 20 pack-yr		At ≥ 10 CPD		Pack-years	Lifetime tar ≥ 3 kg		At ≥ 10 CPD		CPD	Lifetime tar ≥ 3 kg		At ≥ 20 pack-yr	
	No.	*OR*	*No.*	*OR*		*No.*	*OR*	*No.*	*OR*		*No.*	*OR*	*No.*	*OR*
Men														
1–2	359	26.9	289	8.4	1–19	31	6.3	187	3.3	1–10	245	39.8	341	35.7
3–5	549	26.3	327	25.1	20–39	399	18.1	461	15.4	11–20	296	29.0	516	24.0
6–8	380	30.1	223	32.2	40–59	437	31.6	458	32.4	21–40	336	35.2	637	33.6
9+	420	48.4	255	48.9	60+	513	52.4	550	50.7	41+	173	38.9	316	42.1
Women														
1–2	240	29.5	197	27.4	1–19	15	6.6	100	10.7	1–10	134	34.1	198	36.3
3–5	208	33.9	92	35.9	20–39	128	22.4	249	8.2	11–20	88	42.7	272	28.6
6–8	118	42.7	64	45.5	40–59	174	18.2	198	51.3	21–40	85	45.9	233	45.4
9+	81	48.3	36	67.1	60+	105	64.1	115	71.5	41+	19	38.5	57	58.8

OR: odds ratio; CPD: cigarettes smoked per day.

The data in Table 4 suggest that the steady increase in lung cancer incidence observed during the past few decades is more pronounced in women than in men. This difference in time trends cannot be adequately explained by the continued, reduced exposure to cigarette smoking among women relative to men. Whereas the male to female ratio for smoking prevalence, as reflected in the data for 1974–1985, has declined from 1.4 to 1.2, the ratio for lung cancer incidence has declined even more (from 3.7 to 2.3). The relative frequency of small cell carcinoma, the histologic type that is most directly related to smoking, has shown a nearly fourfold increase in women but has remained stable in men during the same time period. Although it is true that the difference in smoking exposure between the sexes has been steadily diminishing, the corresponding difference in lung cancer risk has been decreasing even faster. All of this suggests that women may have a lower threshold for the carcinogenic effect of tobacco smoke.

Potential explanations for this gender-related difference in lung cancer risk may include hormonal, reproductive, and dietary differences, or the observed lower reliability in the responses of women to various items in the questionnaire.[26] Early exposure cannot be a factor because men, on the average, start smoking at a younger age (17 versus 20 years). Difference in body size appears to be unrelated to lung cancer in men[27] and, therefore, could not account for the gender-specific differences in risk.

Differences in Histologic Type

Our data confirm the well-known difference in the attributable risk of cigarette smoking for KI versus KII lung cancer. The associated odds ratios are three to five times lower for KII than for KI. The observed dose–response for KII still implies a cause-and-effect relationship to tar exposure. Thus, lowering tar yield should also reduce the risk for KII, although to a lesser extent.

Limitations of the Data

The tumorgenic effect of tar is clearly cumulative. The proposed tar yield index appears to provide the best estimate of lung cancer risk among smokers. Nevertheless, our results should be qualified on several accounts.

First, the tar yield estimates mentioned in this report were based on figures reported by the Federal Register in 1977 for the earlier data, and 1988[6] for the most recent data. No allowance was made for changes in tar yield that have occurred in specific cigarette brands during the smoking history of each individual. In fact, the average tar and nicotine yield of cigarettes has decreased by more than 50% during the past three decades, and significant changes even affected the chemistry of the smoke of specific brands.[28–30] Therefore, the risk among long-term smokers who smoke heavily is underestimated by our measure of cumulative tar exposure, particularly if those who smoke heavily tend to smoke cigarettes with higher tar yields. We are currently assembling data on the historical tar and nicotine levels of each brand. In future analyses, we will be able to measure lifelong exposure to tar more accurately by linking each brand smoked with its chronologically appropriate tar yield.

Second, exposure is affected by depth and frequency of inhalation, puff volume, and butt length. Accurate, retrospective information on these measures would have improved the validity of our risk estimates, particularly among those who have switched to low-yield cigarettes and who may attempt to compensate for the resultant loss of nicotine.[19–21]

Third, we classify cases of lung cancer as KI or KII because of past limitations of our data regarding the coding of histologic type. Since 1985, we have substi-

tuted the International Classification of Disease (ICD) coding system, which allows us to classify our cases more precisely.

Finally, despite the efforts of skilled interviewers, our data on smoking history are expected to be subject to the usual biases related to differential recall among cases versus controls, lack of knowledge, and wishful thinking on the part of the participants. However, recent testing, through repeat interviews, of the responses recorded in our data shows a high level of internal consistency.[26]

Additional studies are needed to estimate the risk of cancer of the oral cavity, larynx, pancreas, bladder, and esophagus, as well as the risk of other smoking-related conditions such as cardiovascular disease and emphysema. Previous studies have shown no enhanced risk for the development of cardiovascular disease related to low tar/nicotine cigarettes, despite a tendency to compensate for nicotine. Regarding the risk of neoplastic disease, the tar to nicotine ratio requires particular attention. The cumulative, lifelong tar exposure index introduced here can also be effectively applied to relative risk and dose-response estimations related to other cancer sites.

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